SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	*Restylane-L* Injectable Gel
Device Procode:	LMH
Applicant's Name and Address:	Medicis Aesthetics Holdings, Inc. 7720 N Dobson Road Scottsdale, AZ 85256
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P040024/S056
Date of FDA Notice of Approval:	August 30, 2012
Expedited:	Not Applicable

The original PMA (PMA P040024) for *Restylane* was approved on March 25, 2005 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds (NLF). Submucosal implantation for lip augmentation in patients over the age of 21 was added to the indications for *Restylane* in supplement P040024/S051 approved on October 11, 2011. The General and Plastic Surgery Devices Advisory Panel recommended approval of supplement P040024/S051 at the April 27, 2011 meeting. *Restylane-L* was approved in supplement P040024/S039 on January 29, 2010 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as NLFs. The SSEDs to support the NLF and lip indications are available on the CDRH website and are incorporated by reference here. Information from supplement P040024/S039 is included below as a SSED was not required for supplement P040024/S039. The current supplement was submitted to expand the indication for *Restylane-L* Injectable Gel to include submucosal implantation for lip augmentation in patients over the age of 21.

II. INDICATIONS FOR USE

Restylane-L is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Restylane-L is indicated for submucosal implantation for lip augmentation in patients over the age of 21.

III. CONTRAINDICATIONS

- *Restylane-L* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane-L* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane-L* is contraindicated for patients with bleeding disorders.
- *Restylane-L* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.
- *Restylane-L* should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane-L* labeling.

V. DEVICE DESCRIPTION

Restylane-L contains 0.3% lidocaine and is a gel of hyaluronic acid (HA) isolated from a *Streptococcus* species that is chemically crosslinked with 1,4-butanediol diglycidyl ether (BDDE), stabilized, and suspended in phosphate buffered saline at pH = 7 and a concentration of 20 mg/mL. *Restylane-L* is a transparent, viscous, and sterile gel that is supplied in a disposable glass syringe. The product is approved in fill sizes of 0.5, 1, and 2 mL. The syringe is co-packed in a blister together with sterile 29 G or 30 G needle(s).

The HA has a molecular weight of about one million and is stabilized by adding a minimum amount of BDDE to allow formation of a three-dimensional HA molecular network. The chemical stabilizing process does not change the polyanionic character of the polysaccharide chain.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patients frequently seek correction of facial contour deformities that are: (1) age-related loss of facial fat or weakening of underlying supportive structures; (2) sun damage in non-pigmented skin; or, (3) related to specific diseases or their treatments that may cause facial wasting, scarring, or structural damage (*e.g.* prior surgery, anorexia, acne vulgaris, collagen vascular disease). Treatment of photo-damaged skin, with its associated wrinkling and changes in texture and pigmentation, is often accomplished by use of topical moisturizing creams (some of which may contain pharmaceuticals, such as sunscreens or retinoids), chemical or mechanical peeling procedures, or laser resurfacing. These methodologies typically affect epidermal quality but do not treat underlying structural issues. Deeper wrinkles, folds, scars, and other lesions are often treated with surgery (*e.g.* scar revision, blepharoplasty, face lift, rhytidectomy, permanent silastic implants). Other than implants, these methodologies have the advantage of reducing redundant

skin but do not restore the youthful look associated with abundant soft tissue support. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Restylane was first approved for marketing and sale in September 1996 in the European Union, Iceland, Liechtenstein and Norway (EES). The product has since been approved in several countries worldwide. *Restylane* was approved in the United States (U.S.) under PMA P020023 (submitted by Q-Med) on December 12, 2003, and under PMA P040024 (submitted by Medicis) on March 25, 2005. *Restylane-L* was approved as a supplement to the *Restylane* PMA P040024/S039 on January 29, 2010. *Restylane-L* has not been removed from the marketplace for any reasons related to safety, effectiveness, patient or physician complaint, or dissatisfaction.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of *Restylane* for lip augmentation was evaluated in three premarket studies. Table 1 provides a list of the potential adverse effects (AEs, *i.e.* complications) associated with the use of the device.

Table 1. Potential Adverse Effects Associated with *Restylane* Injection for Lip Augmentation

Acne
Aphthous Stomatitis
Broken Capillaries
Burning Sensation
Cheilitis
Contusion (Bruising/Ecchymosis)
Death
Dermatitis
Device Dislocation
Discolouration
Erythema
Extrusion of Device
Eye Disorders
Fistula/Leakage
Granuloma/Foreign Body Reaction
Headache
Herpes Simplex
Hyperpigmentation
Hypersensitivity (Allergic Reaction and Anaphylactic Shock)
Inflammation
Infection/Abscess
Ischemia/Necrosis
Lip Blister
Lip Discoloration

Lip Disorder
Lip Dry
Lip Exfoliation
Lip Pain
Lip Swelling
Lip Ulceration
Mass Formation
Muscle Disorders
Nasopharyngitis
Necrosis
Numbness
Oral Dysesthesia
Pain
Papules/Nodules
Paraesthesia Oral
Pruritus
Rash
Scar/Scab/Skin Atrophy
Skin Exfoliation (includes Sloughing of the Skin, Peeling, Desquamation, and Superficial Desquamation)
Swelling
Swollen Tongue
Tenderness
Urticaria

In pivotal study MA-1300-15 there were five serious adverse events (SAEs) reported in *Restylane*-treated patients, i.e., diverticulitis (n = 1), pneumonia and pneumococcal infection (n = 1), lumbar spinal stenosis (n = 1), and transient ischemic attack (n = 1).

In pilot study MA-1300-13k there were two SAEs. A death occurred when a patient (with a medical history indicating hypothyroidism) experienced cardiac arrest on day 29 resulting from a thyroid neoplasm. Another subject (whose medical history included rheumatoid arthritis, peripheral neuropathy, and hyperlipidemia) was hospitalized for severe cellulitis of the left lower extremity that was refractory to antibiotic therapy. Both SAEs were considered unrelated to the study device.

The safety of *Restylane-L* for mid-to-deep dermal implantation for the correction of moderate to severe nasolabial folds was evaluated in one premarket study. In Study MA-1100-001 there were no SAEs or serious incident reports during the study and no AE resulted in subject discontinuation.

For the specific adverse events that occurred in the clinical studies, please see Section X Part D below.

IX. SUMMARY OF PRECLINICAL STUDIES

The supplement did not contain any manufacturing information or preclinical testing because no change in product manufacture or specification was proposed. Instead, the data previously presented in PMA P040024 were sufficient to support the new proposed indication for use.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant provided data from a clinical study performed in the US under IDE # G080151 to establish a reasonable assurance of safety and effectiveness of wrinkle treatment with *Restylane-L* for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. The SSED for P040024/S051 describes three clinical studies of *Restylane* performed in the US under IDE # G060011 and in Canada to establish a reasonable assurance of safety and effectiveness for submucosal implantation for lip augmentation in patients over the age 21. Data from these clinical studies were the basis for the PMA approval decision. Information about the clinical study from supplement P040024/S039 as well as a summary of the study design for P040024/S051 is presented below.

A Randomized Double-Blind Study Comparing Safety and Tolerability of *Restylane* with and without Addition of 0.3% Lidocaine HCl during the Correction of Nasolabial Folds (MA-1100-001, P044024/S039)

A. Study Design

Sixty patients were treated between January 12, 2009 and February 24, 2009 at three investigational sites in the United States. The intent of the prospective, 1:1 randomized, multi-center, double-blind, one-arm clinical study was to demonstrate a pain relieving effect during treatment when lidocaine hydrochloride was added to *Restylane*. Inclusion criteria included having the same wrinkle severity rating scale (WSRS) score at both NLFs (both Moderate [3] or both Severe [4]) as assessed during screening by the investigator. Patients were randomized to *Restylane-L* or *Restylane* treatment in a "within-patient" model of bilateral NLF correction, with one treatment assigned to one side of the face and the other treatment to the remaining side. Both patients and treating physicians were blinded; evaluating physicians were also independent and blinded. Pain was assessed by each patient for each treatment site independently on the Visual Analog Scale (VAS) at the end of injection and at 15-minute intervals for 60 minutes post-treatment. Patient assessment of appearance using the Global Aesthetic Improvement Scale (GAIS) was performed at the day 14 visit. Safety was studied with 14-day follow-up. The study recruited a minimum of 25% of subjects with darker skin types, or Fitzpatrick Skin Types IV, V, or VI (minimum of 10% skin type IV and minimum of 15% skin type V or VI).

WSRS scores as defined in Table 2 were assigned by the investigator to evaluate the visual appearance of the NLFs at screening to assess inclusion criteria.

Table 2. Wrinkle Severity Rating Scale (WSRS)

Score	Description
5	**Extreme:** Extremely deep and long folds; detrimental to facial appearance. 2-4 mm visible v-shaped fold when stretched. Unlikely to have satisfactory correction with injectable implant alone.
4	**Severe:** Very long and deep folds; prominent facial feature. Less than 2 mm visible fold when stretched. Significant improvement is expected from injectable implant
3	**Moderate:** Moderately deep folds; clear facial feature visible at normal appearance but not when stretched. Excellent correction is expected from injectable implant.
2	**Mild:** Shallow but visible fold with a slight indentation; minor facial feature. Implant is expected to produce a slight improvement in appearance.
1	**Absent:** no visible fold; continuous skin line

The VAS was a straight, 100 mm long line with the left end representing no pain and the right end representing the worst pain. For each side of the face, subjects were asked to mark the location on the line that represented their level of pain. The distance along the line from the no pain end to the marked location was measured and expressed in units of mm.

The GAIS scoring system described in Table 3 was assigned by each subject to assess the visual appearance of their NLFs on day 14.

Table 3. Global Aesthetic Improvement Scale (GAIS)

Score	Rating	Definition
4	Very Much Improved	Optimal cosmetic result for the implant in this subject.
3	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
2	Improved	Obvious improvement in appearance from the initial condition.
1	No Change	The appearance is essentially the same as baseline.
0	Worse	The appearance is worse than the original condition.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the MA-1100-001 study was limited to patients who met the following inclusion criteria: males or non-pregnant, non-breast-feeding females, 18 to 65 years of age; seeking augmentation therapy for correction of bilateral NLFs; had the same WSRS score at both NLFs (either both Moderate [3] or both Severe [4]); had the ability to understand and comply with the requirements of the study; willing to abstain from exclusionary procedures for the duration of the study; willing to give written informed consent to participate in the study; and women of childbearing potential willing to use an acceptable form of birth control during the study period.

Patients were not permitted to enroll in the MA-1100-001 study if they met any of the following exclusion criteria: active or chronic skin disease, inflammation or related conditions, near or on the NLFs; had undergone procedures based on active dermal response (*e.g.* laser or chemical peeling procedures) within six months prior to study entry; use of any facial tissue augmenting therapy with non-permanent filler or aesthetic facial surgical therapy within nine months prior to

study entry; use of topical or systemic pain-relieving medication or other pain relieving technique (*e.g.* ice) from midnight on the day of treatment until after the last VAS assessment; permanent implant placed in the NLF area; concomitant anticoagulant therapy or antiplatelet therapy within two weeks of treatment, or a history of bleeding disorders; had previously experienced unanticipated adverse effects when treated with hyaluronic acid based products; had previously experienced allergic reactions when treated with lidocaine; any condition, which in the opinion of the Investigator, made the subject unsuitable for inclusion; cancerous or pre-cancerous lesions in the area to be treated; and use of any investigational drugs or devices within 30 days prior to randomization.

2. Follow-up Schedule

Subject participation consisted of screening, treatment within 14 days of screening, and follow-up on day 14 post-treatment. Subjects were provided with a diary in which to document symptoms for 14 days after treatment.

Before treatment, WSRS scores were assigned to both the right and left NLFs by the investigator to assess inclusion criteria. After treatment, the objective parameters measured during the study included the following: (1) pain assessment by the subject for each treatment site at the end of injection and at 15-minute intervals for 60 minutes post-treatment using VAS and (2) assessment of appearance by the subject at day 14 post-treatment using GAIS. Adverse events and complications were recorded at all visits.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary objective was to compare the safety profiles of *Restylane-L* and *Restylane* by identifying the point incidence of: all local adverse events as reported by healthcare professionals, all systemic adverse events (related and unrelated), and the occurrence and extent of symptoms as recorded by subjects in a diary for 14 days post-treatment. Subjects were instructed to record the presence of bruising, redness, swelling, pain, tenderness, itching, or other symptoms and assess the extent of the symptoms as tolerable, affects daily activities, or disabling.

With regards to effectiveness, the primary endpoint was the proportion of subjects that had a within-subject difference in the VAS (*Restylane – Restylane-L*) pain assessment of at least 10 mm at injection together with a 95% confidence interval. The objective was to show that the confidence interval lay above 50%. The following additional effectiveness endpoints were evaluated: (1) the proportion of subjects that had a within-subject difference in VAS pain assessment of at least 10 mm at post-treatment time points (15, 30, 45, and 60 minutes after injection) together with a 95% confidence interval; (2) the mean VAS pain assessment by treatment and within-subject difference in VAS pain assessment at each time point (at injection and 15, 30, 45, and 60 minutes after injection; (3) comparison of VAS pain assessment between *Restylane-L* and *Restylane* at each time point; and (4) subject assessment on GAIS by treatment using descriptive statistics.

B. Accountability of PMA Cohort

Sixty patients enrolled in the study and all patients completed the study.

C. Study Population Demographics and Baseline Parameters

There were 60 total subjects enrolled and randomized with a mean age of 52.1 years (Table 4). The study included 32 subjects with darker skin types based on classification of Fitzpatrick Skin Types IV, V, or VI (21/60 or 35% Type IV and 11/60 or 18.3% Type V and VI). The patient population consisted predominantly of Caucasian females.

Table 4. Demographics of study subjects

Parameter	N = 60 Subjects
Age (years)	
Mean	52.1
SD	6.6
Median	52.7
Minimum, Maximum	37.6, 64.2
Gender	
Female	58 (96.7%)
Male	2 (3.3%)
Race/Ethnicity	
White	34 (56.7%)
Hispanic/Latino	21 (35.0%)
Black or African American	3 (5.0%)
Asian	1 (1.7%)
Other	1 (1.7%)
Fitzpatrick Skin Type	
I+II+III	28 (46.7%)
IV	21 (35.0%)
V+VI	11 (18.3%)
Baseline WSRS	
Score 3	30 (50.0%)
Score 4	30 (50.0%)
Prior cosmetic or aesthetic procedures	
No	46 (76.7%)
Yes	14 (23.3%)

D. Safety and Effectiveness Results

1. Safety Results

Safety was assessed 14 days after device implantation into the NLFs of 60 subjects treated with *Restylane-L* on one side of the face and *Restylane* on the other. Adverse effects are reported in Tables 5 to 9.

Adverse effects that occurred in the PMA clinical study:

There were no SAEs or serious incident reports during the study and no AE resulted in subject discontinuation. AE data collected by investigators at follow-up visits and adverse outcome data documented by subjects in their diaries were not merged and are counted and displayed separately. The total number of all AEs, both related and unrelated to treatment, as well as the number of subjects with these events are presented in Table 5. A total of 253 AEs were reported for 46 subjects (76.7%). The majority of these events (242/253) were considered to be related to treatment and occurred in 42 subjects. The severity and duration of device related AEs for the *Restylane-L* and *Restylane* treated NLFs are shown in Tables 6 and 7. Similar numbers of AEs were reported for both the *Restylane-L* and *Restylane* sides of the face, with 123 reported for *Restylane-L* and 118 for *Restylane*. Three subjects had implant site masses of mild severity, two on the *Restylane* side and one on the *Restylane-L* side. One subject experienced vasospasm of moderate intensity on the *Restylane-L* side of the face with the following symptoms: right-sided sinus secretions, some with dried blood; sinus irritation; sharp pain inside right nostril; and right eye swollen and crusty with secretions. One AE described as being light headed was determined to be related to treatment, but was classified as systemic and not related to a specific site. Treatments for four reactions were still ongoing at day 14, two reactions each for *Restylane-L* and *Restylane*. The most commonly reported AEs for *Restylane-L* were injection site erythema, implant site swelling, injection site pain, implant site hematoma, and implant site pain. The most commonly reported AEs for *Restylane* were injection site erythema, injection site pain, implant swelling, implant site hematoma, and implant site pain. There were 11 AEs experienced by 9 subjects that were determined to be unrelated to treatment. The number of adverse outcomes, intensity of adverse outcomes, and duration of symptoms collected from subject diaries are summarized in Tables 8 and 9.

Table 5. All adverse events identified by investigators

Primary System Organ Class *Preferred Term*	No. of subjects		No. of events
	n	%	
Cardiac disorders			
Tachycardia	1	1.7	1
General disorders and administration site conditions			
Implant site haematoma	29	48.3	42
Implant site mass	3	5.0	3
Implant site pain	22	36.7	35
Implant site swelling	25	41.7	46
Injection site erythema	29	48.3	55
Injection site pain	28	46.7	49
Injection site pruritus	8	13.3	10
Infections and infestations			
Influenza	1	1.7	1
Sinusitis	1	1.7	1
Injury, poisoning and procedural complications			
Injury	1	1.7	1
Nervous system disorders			
Dizziness	1	1.7	1
Headache	3	5.0	4
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	3	5.0	3
Vascular disorders			
Vasospasm	1	1.7	1
All	46	76.7	253

Source: Statistical Report: Appendix 16.1.9, Table 1.40, Appendices 16.2.7.1 – 16.2.7.4
% = percentage of subjects in Safety population

Table 6. Severity of device related AEs identified by investigators

System Organ Class *Preferred Term*	*Restylane L.* Grade of Intensity				*Restylane* Grade of Intensity			
	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
General disorders and administration site conditions								
Implant site haematoma	18	5	.	23	15	4	.	19
Implant site mass	1	.	.	1	2	.	.	2
Implant site pain	12	5	.	17	15	3	.	18
Implant site swelling	14	10	.	24	16	6	.	22
Injection site erythema	24	4	.	28	24	3	.	27
Injection site pain	19	4	.	23	22	4	.	26
Injection site pruritus	6	.	.	6	4	.	.	4
Vascular disorders								
Vasospasm	.	1	.	1	.	.	.	.
ALL*	94	29	.	123	98	20	.	118

Source: Statistical Report: Appendix 16.1.9, Table 1.42, Appendices 16.2.7.1 – 16.2.7.4
*One event in Subject 1012 was classified as systemic and not related to a specific treatment site. The diagnosis of the event was 'Light headedness', and the maximum intensity was 'Mild'.

Table 7. Duration of device related AEs identified by investigators from day 1 to day 14 post-treatment

Primary System Organ Class *Preferred Term*	*Restylane L.* Duration (days)							*Restylane* Duration (days)						
	units	n	Mean	Std	Min	Median	Max	units	n	Mean	Std	Min	Median	Max
General disorders and administration site conditions														
Implant site haematoma	0	23	4.7	2.8	1	4.0	11	0	19	5.8	2.9	2	5.0	12
Implant site mass	1	0	.	.	.	.	.	2	0	.	.	.	.	.
Implant site pain	0	17	3.1	1.6	1	3.0	7	0	18	2.6	1.6	1	2.0	7
Implant site swelling	0	24	4.9	1.8	2	4.5	9	0	22	4.6	2.6	2	4.0	13
Injection site erythema	0	28	3.3	2.0	1	2.5	8	0	27	3.2	1.9	1	2.0	8
Injection site pain	0	23	4.3	2.3	2	4.0	12	0	26	4.8	3.9	1	4.0	20
Injection site pruritus	0	6	2.5	1.4	1	2.0	5	0	4	2.8	1.7	1	2.5	5
Vascular disorders														
Vasospasm	1	0	.	.	.	.	.	.	.	.	.	.	.	.
ALL	2	121	4.0	2.2	1	4.0	12	2	116	4.1	2.9	1	4.0	20

Source: Statistical Report: Appendix 16.1.9, Table 1.43, Appendices 16.2.7.1 – 16.2.7.4
* AE is still ongoing at study end.
Abbreviations: n = number of subjects, std = standard deviation; Min = minimum; Max = maximum

Table 8. Number of adverse outcomes and intensity of symptoms after treatment – subject diary

	Restylane L.	*Restylane*	*Restylane L.*				*Restylane*			
	Total subjects reporting symptoms n (%)	Total subjects reporting symptoms n (%)	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	35 (58.3)	31 (51.7)	25 (41.7)	30 (50.0)	4 (6.7)	1 (1.7)	29 (48.3)	27 (45.0)	3 (5.0)	1 (1.7)
Itching	8 (13.3)	7 (11.7)	52 (86.7)	7 (11.7)	1 (1.7)	0 (0.0)	53 (88.3)	7 (11.7)	0 (0.0)	0 (0.0)
Pain	27 (45.0)	27 (45.0)	33 (55.0)	24 (40.0)	2 (3.3)	1 (1.7)	33 (55.0)	26 (43.3)	1 (1.7)	0 (0.0)
Redness	30 (50.0)	28 (46.7)	30 (50.0)	27 (45.0)	2 (3.3)	1 (1.7)	32 (53.3)	28 (46.7)	0 (0.0)	0 (0.0)
Swelling	40 (66.7)	36 (60.0)	20 (33.3)	29 (48.3)	10 (16.7)	1 (1.7)	24 (40.0)	29 (48.3)	7 (11.7)	0 (0.0)
Tenderness	41 (68.3)	39 (65.0)	19 (31.7)	38 (63.3)	2 (3.3)	1 (1.7)	21 (35.0)	38 (63.3)	1 (1.7)	0 (0.0)
Other[3]	4 (6.7)	7 (11.7)	NA	NA	NA	NA	NA	NA	NA	NA

Source: Statistical Report: Appendix 16.1.9, Table 1.37, Appendices 16.2.7.7 – 16.2.7.8
n/N = n/number of subjects in safety population
[1]Missing values are not reported.
[2]Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[3] Other included symptoms of vasospasm, lump/bump, small blue mark, and sinus drip. Diary entries of throbbing/flushing, cold, chafing, dryness, shadow, headache, bad back, and neck pain could not be associated with a particular product.

Table 9. Duration of symptoms after treatment – subject diary

	Restylane L	*Restylane*	*Restylane L*				*Restylane*			
	Total subjects reporting symptoms n (%)	Total subjects reporting symptoms n (%)	Number of days[2]				Number of days[2]			
			1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Bruising	35 (58.3)	31 (51.7)	3 (8.6)	28 (80.0)	4 (11.4)	0 (0.0)	0 (0.0)	25 (80.6)	6 (19.4)	0 (0.0)
Itching	8 (13.3)	7 (11.7)	7 (87.5)	1 (12.5)	0 (0.0)	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)
Pain	27 (45.0)	27 (45.0)	13 (48.1)	11 (40.7)	1 (3.7)	2 (7.4)	15 (55.6)	11 (40.7)	0 (0.0)	1 (3.7)
Redness	30 (50.0)	28 (46.7)	10 (33.3)	17 (56.7)	2 (6.7)	1 (3.3)	9 (32.1)	18 (64.3)	1 (3.6)	0 (0.0)
Swelling	40 (66.7)	36 (60.0)	4 (10.0)	29 (72.5)	7 (17.5)	0 (0.0)	8 (22.2)	21 (58.3)	5 (13.9)	2 (5.6)
Tenderness	41 (68.3)	39 (65.0)	13 (31.7)	20 (48.8)	5 (12.2)	3 (7.3)	9 (23.1)	25 (64.1)	3 (7.7)	2 (5.1)
Other[3]	4 (6.7)	7 (11.7)	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)	1 (14.3)	5 (71.4)	0 (0.0)	1 (14.3)

Source: Statistical Report: Appendix 16.1.9, Table 1.38, Appendices 16.2.7.7 – 16.2.7.8
% = n/number of subjects in safety population
[1] Missing values are not reported.
[2] Percentage calculated using number of subjects reporting symptoms.
[3] Other included symptoms of vasospasm, lump/bump, small blue mark, and sinus drip. Diary entries of throbbing/flushing, cold, chafing, dryness, shadow, headache, bad back, and neck pain could not be associated with a particular product.

2. Effectiveness Results

The analysis of effectiveness was based on 60 evaluable subjects at the 14 day time point. Key effectiveness outcomes are presented in Tables 10 to 13. The mean volumes of *Restylane-L* and *Restylane* injected into NLFs were 1.24 ml and 1.23 ml, respectively (Table 10).

Assessment of pain was made by subjects at the time of injection as well as 15, 30, 45, and 60 minutes post-treatment using the VAS. The primary effectiveness endpoint was met as 71.7% of subjects had a within-subject difference in the VAS (*Restylane – Restylane-L*) pain assessment of at least 10 mm at injection (Table 11). At 15 minutes post-treatment, 46.7% of subjects had a within-patient difference in VAS of at least 10 mm. At the time of treatment, the mean VAS score for *Restylane-L* was 14.7 mm compared to 44.9 mm for *Restylane*. For both treatments, all pain scores decreased over time for 60 minutes after treatment. The mean within-subject difference in VAS was statistically larger than zero at all time points (Table 12, $p < 0.001$).

The GAIS was used to assess the subject's satisfaction with the visual appearance of their NLFs after wrinkle treatment. At day 14, improvements from baseline were reported by all subjects for the *Restylane-L* side of the face and 98.3% of subjects for the *Restylane* side (Table 13).

Table 10. Volume of *Restylane-L* and *Restylane* injected into NLFs

Treatment	Volume (mL)					
	n	Mean	Std	Min	Median	Max
***Restylane-L* per NLF**	60	1.24	0.54	0.60	1.00	3.00
***Restylane* per NLF**	60	1.23	0.55	0.60	1.00	3.00
Difference within patient*	60	-0.01	0.18	-0.50	0.00	0.40

* *Restylane* volume - *Restylane-L* volume
Abbreviations: n = number of patients; std = standard deviation; Min = minimum; Max = maximum

Table 11. Subjects with at least a 10 mm difference in VAS (*Restylane - Restylane-L*)

Timepoint	No. of subjects with assessments**	Number of subjects with Δ ≥ 10 mm			
		n	%	95% LCL	95% UCL
Treatment*	60	43	71.7	58.6	82.5
15 Minutes	60	28	46.7	33.7	60.0
30 Minutes	60	17	28.3	17.5	41.4
45 Minutes	60	10	16.7	8.3	28.5
60 Minutes	60	4	6.7	1.8	16.2

Source: Statistical Report: Appendix 16.1.9, Table 1.23, Appendix 16.2.6.1
*Primary endpoint
**Denominator (N), % = 100*n/N
UCL=upper confidence limit; LCL=lower confidence limit

Table 12. Mean VAS scores assigned by subjects to describe the level of pain at each time point after treatment (*Restylane – Restylane-L*)

Timepoint	VAS pain by treatment (mm)		VAS difference (mm)*	P-value**
	Restylane L	*Restylane*		
Treatment	14.7	44.9	30.3	<0.001
15 Minutes	6.1	23.2	17.2	<0.001
30 Minutes	2.5	11.7	9.2	<0.001
45 Minutes	1.4	7.0	5.6	<0.001
60 Minutes	1.0	3.2	2.2	<0.001

Source: Statistical Report: Appendix 16.1.9, Tables 1.24 - 1.26, Appendix 16.2.6.1
*Within-subject difference (*Restylane* side - *Restylane L* side) **One-sample T-test

Table 13. GAIS evaluation by subjects at day 14 for *Restylane-L* and *Restylane*

Category	GAIS			
	Restylane L		*Restylane*	
	n	%	n	%
Very Much Improved (4)	17	28.3	18	30.0
Much Improved (3)	29	48.3	29	48.3
Improved (2)	14	23.3	12	20.0
No Change (1)	.	0.0	1	1.7
Worse (0)	.	0.0	.	0.0

Source: Statistical Report: Appendix 16.1.9, Table 1.27, Appendix 16.2.6.2

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Randomized Evaluator Blinded Not Treatment Controlled Study of the Effectiveness and Safety of *Restylane* in the Augmentation of Soft Tissue Fullness of the Lips Pivotal Study (MA-1300-15, P040024/S051)

The trial was a multi-center, two-arm study with a 3:1 randomization to Treatment and No Treatment cohorts. After treatment, patients attended clinical visits at 72 hours and 2, 4, 8, 12, 16, 20, 24 weeks after *Restylane* injection as well as 2 and 4 weeks after a week 24 *Restylane* re-treatment. The primary effectiveness endpoint compared the differences in the live Blinded Evaluators' Medicis Lip Fullness Scale (MFLS) assessments at week 8 post-treatment with the Treating Investigators' baseline MLFS score. Separate upper and lower lip evaluations were performed (as co-primary endpoints) and treatment success was defined as at least a one grade increase in MLFS for both the upper and lower lips. The proportion of Responders (i.e., at least a one grade increase from baseline to week 8 MLFS score for both the upper and lower lips) were calculated using a Fisher's Exact Test.

A No Treatment cohort was the control, because there was no FDA approved therapy for lip augmentation. To maintain masking, Control subjects did not receive *Restylane* injections until week 24. Patients were treated between July 20, 2009 and May 7, 2010. The database for this PMA supplement reflected data collected through June 1, 2010 and included 180 patients. See the SSED for P040024/S051 for more information.

B. Lidocaine

Lidocaine was initially approved by the FDA as a drug on Nov. 19, 1948 and is a commonly used local anesthetic with 65 years of postmarket clinical experience in the US. Lidocaine is commonly injected into the face for surgery and is used in the face, head, and neck at concentrations of 0.5-2% for injection and 4% for topical application. The concentration of lidocaine in *Restylane-L* is 0.3%, which is the same as other approved demal fillers. For normal healthy adults, the individual maximum recommended dose of lidocaine should not exceed 4.5 mg/kg (2 mg/lb) of body weight, and it is recommended that the maximum total dose does not exceed 300 mg.

C. Relevant Postmarket Experience

Review of the sponsor's global postmarketing safety database and the FDA Manufacturer and User Facility Device Experience database (MAUDE) were performed to compare reported adverse events for *Restylane-L* to those for *Restylane* and identify additional safety information about the previous off-label use of *Restylane-L* for lip augmentation.

Table 14. *Restylane-L* and *Restylane* Adverse Events Related to NLF and Lip Injections from 01/01/2007 to 12/31/2011

	Restylane				*Restylane-L*			
	NLF		Lip		NLF		Lip	
	No.	%	No.	%	No.	%	No.	%
MASS/INDURATION	82	10.6%	87	9.7%	15	8.5%	6	3.9%
SWELLING	79	10.2%	154	17.1%	16	9.0%	47	30.9%
DEVICE INEFFECTIVE	69	8.9%	113	12.6%	12	6.8%	16	10.5%
ERYTHEMA	59	7.7%	29	3.2%	13	7.3%	4	2.6%
NON DERMATOLOGICAL EVENTS	70	9.1%	77	8.6%	18	10.2%	8	5.3%
BRUISING/BLEEDING	52	6.7%	55	6.1%	7	4.0%	16	10.5%
MEDICAL DEVICE IMPLANTATION	42	5.4%	76	8.5%	3	1.7%	4	2.6%
DISCOLOURATION	38	4.9%	23	2.6%	6	3.4%	5	3.3%
PAIN/TENDERNESS	42	5.4%	64	7.1%	10	5.6%	10	6.6%
EXTRUSION OF DEVICE	29	3.8%	14	1.6%	0	0.0%	0	0.0%
ISCHEMIA/NECROSIS	30	3.9%	17	1.9%	13	7.3%	3	2.0%
INFECTION/ABSCESS	20	2.6%	19	2.1%	20	11.3%	3	2.0%
PAPULES/NODULES	26	3.4%	24	2.7%	10	5.6%	8	5.3%
INJECTION SITE REACTIONS	12	1.6%	18	2.0%	7	4.0%	1	0.7%
CAPILLARY DISORDER	10	1.3%	1	0.1%	3	1.7%	0	0.0%
INFLAMMATION	13	1.7%	5	0.6%	0	0.0%	3	2.0%
PRODUCT QUALITY ISSUE	8	1.0%	6	0.7%	0	0.0%	0	0.0%
RASH	9	1.2%	3	0.3%	1	0.6%	0	0.0%
HYPERSENSITIVITY	9	1.2%	25	2.8%	3	1.7%	10	6.6%
PRURITUS	7	0.9%	8	0.9%	2	1.1%	0	0.0%
ACNE	7	0.9%	2	0.2%	1	0.6%	0	0.0%
DEVICE DISLOCATION	7	0.9%	5	0.6%	0	0.0%	1	0.7%
OTHER DERMATOLOGICAL EVENTS	7	0.9%	17	1.9%	2	1.1%	1	0.7%
HERPES	5	0.6%	15	1.7%	0	0.0%	2	1.3%
SCAR/SCAB/SKIN ATROPHY	7	0.9%	10	1.1%	7	4.0%	1	0.7%
ACCIDENTAL EXPOSURE	3	0.4%	0	0.0%	4	2.3%	0	0.0%
EYE DISORDERS	5	0.6%	2	0.2%	1	0.6%	0	0.0%
GRANULOMA/FOREIGN BODY REACTION	4	0.5%	4	0.4%	0	0.0%	0	0.0%
URTICARIA	3	0.4%	1	0.1%	0	0.0%	0	0.0%
DEVICE MISUSE	3	0.4%	6	0.7%	1	0.6%	0	0.0%
INVESTIGATIONS	3	0.4%	0	0.0%	0	0.0%	0	0.0%
SWELLING FACE	2	0.3%	2	0.2%	0	0.0%	0	0.0%
DERMATITIS	1	0.1%	5	0.6%	1	0.6%	0	0.0%
FISTULA/LEAKAGE	3	0.4%	1	0.1%	0	0.0%	1	0.7%
MUSCLE DISORDERS	4	0.5%	1	0.1%	0	0.0%	0	0.0%
BLISTERS/VESICLES	1	0.1%	8	0.9%	0	0.0%	1	0.7%
PROCEDURAL COMPLICATIONS	0	0.0%	0	0.0%	1	0.6%	1	0.7%
SWOLLEN TONGUE	0	0.0%	1	0.1%	0	0.0%	0	0.0%

In a review of the MAUDE database for Medical Device Reports (MDRs), 31 MDRs were reported for *Restylane-L*. The types of AEs reported for *Restylane-L* were similar to those observed during clinical studies of *Restylane-L* and *Restylane*. Reported adverse events included the following: mass/lesions under the skin, infection/abscess (some requiring incision and drainage), hypersensitivity, vascular accidents, skin discoloration, bruising, blanching, necrosis, and scarring.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of data from two clinical studies. The data provide a reasonable assurance that *Restylane-L* is effective for submucosal implantation for lip augmentation in patients over the age of 21. The specific conclusions from the clinical studies are outlined below.

A Randomized Double-Blind Study Comparing Safety and Tolerability of *Restylane* with and without Addition of 0.3% Lidocaine HCl during the Correction of Nasolabial Folds (MA-1100-001, P044024/S039)

- The study met the pre-specified primary effectiveness criterion as 71.7% of subjects had a within-subject difference in the VAS (*Restylane – Restylane-L*) pain assessment of at least 10 mm at injection for NLFs. At 15 minutes post-treatment, 46.7% of subjects had a within-patient difference in VAS of at least 10 mm. At the time of treatment, the mean VAS score for *Restylane-L* was 14.7 mm compared to 44.9 mm for *Restylane*. For both treatments, all pain scores decreased over time for 60 minutes after treatment. The mean within-subject difference in VAS was statistically larger than zero at all time points ($p < 0.001$).

- At day 14 post-treatment, improvements compared to baseline in the visual appearance of NLFs as assessed using GAIS were reported by all subjects for the *Restylane-L* side of the face and 98.3% of subjects for the *Restylane* side.

Randomized Evaluator Blinded Not Treatment Controlled Study of the Effectiveness and Safety of *Restylane* in the Augmentation of Soft Tissue Fullness of the Lips Pivotal Study (MA-1300-15, P040024/S051)

- The study met the pre-specified primary effectiveness criterion in that the difference in the proportion of Responders for upper and lower lips, separately and combined, for *Restylane* and No Treatment cohorts was statistically significant ($p < 0.001$) in favor of *Restylane*. In the *Restylane* group at week 8, 94.8% (127/134) of the subjects were upper lip Responders and 94.3% (115/122) of the subjects were lower lip Responders. For upper and lower lips combined, 92.6% (125/135) of the subjects responded to *Restylane* at week 8. In the No Treatment group, 36.4% (upper lips) and 38.5% (lower lips) of the subjects had Blinded Evaluator MLFS ratings that were at least one grade higher than baseline and 28.9% of the No Treatment subjects were Responders for both upper and lower lips combined.

- The study met the pre-specified secondary effectiveness endpoints for the proportion of Responders when comparing *Restylane* to No Treatment cohorts based on: 1) the Blinded Evaluators' MLFS ratings from weeks 12 to 24; 2) the Treating Investigators' MLFS ratings from Weeks 2-24; 3) the Independent Photographic Reviewers' MLFS ratings from Weeks 4-24; 4) the Treating Investigators' GAIS scores; and 5) the Subjects' GAIS scores.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the two clinical studies identified below to support PMA approval. The data provide a reasonable assurance that *Restylane-L* is safe for submucosal implantation for lip augmentation in patients over the age of 21. The specific conclusions from the clinical studies are outlined below.

A Randomized Double-Blind Study Comparing Safety and Tolerability of *Restylane* with and without Addition of 0.3% Lidocaine HCl during the Correction of Nasolabial Folds (MA-1100-001, P044024/S039)

- There were no SAEs or serious incident reports during the study on NLFs and no AE resulted in subject discontinuation.

- A total of 253 AEs were reported for 46 subjects (76.7%). The majority of these events (242/253) were considered to be related to treatment and occurred in 42 subjects. Similar numbers of AEs were reported for both the *Restylane-L* and *Restylane* sides of the face, with 123 reported for *Restylane-L* and 118 for *Restylane*. Three subjects had implant site masses of mild severity, two on the *Restylane* side and one on the *Restylane-L* side. One subject experienced vasospasm of moderate intensity on the *Restylane-L* side of the face with the following symptoms: right-sided sinus secretions, some with dried blood; sinus irritation; sharp pain inside right nostril; and right eye swollen and crusty with secretions. One AE described as being light headed was determined to be related to treatment, but was classified as systemic and not related to a specific site. Treatments for four reactions were still ongoing at day 14, two reactions each for *Restylane-L* and *Restylane*.

- The most commonly reported AEs for *Restylane-L* were injection site erythema, implant site swelling, injection site pain, implant site hematoma, and implant site pain. The most commonly reported AEs for *Restylane* were injection site erythema, injection site pain, implant swelling, implant site hematoma, and implant site pain.

- There were 11 AEs experienced by 9 subjects that were determined to be unrelated to treatment.

Randomized Evaluator Blinded Not Treatment Controlled Study of the Effectiveness and Safety of *Restylane* in the Augmentation of Soft Tissue Fullness of the Lips Pivotal Study (MA-1300-15, P040024/S051)

- The majority of treatment emergent AEs (TEAEs) were mild in intensity (i.e., 672/795 (85%) and 264/267 (99%)), after the first and second treatments, respectively. For receiving their first *Restylane* treatment series a mean TEAE duration of 15.6 days was observed and for subjects receiving their second *Restylane* treatment series at week 24 a mean duration of 10.4 days was observed.

- Four serious adverse events not related to the study device were reported in the *Restylane* treatment group, i.e., diverticulitis (n = 1), pneumonia and pneumococcal infection (n = 1), lumbar spinal stenosis (n = 1) and transient ischemic attack (n = 1).

- The frequency of adverse outcomes reported in the 14 day patient diary was 97.1% (upper lip) and 94% (lower lip) for subjects receiving their first *Restylane* treatment. The commonly reported adverse outcomes (*e.g.* pain, swelling, tenderness, contusion (bruising/ecchymosis), and erythema) were anticipated and attributed to the procedure or *Restylane*. Onset was typically within a day of treatment and resolution usually occurred within 15 days or less. 15% of the patients experienced adverse outcomes (typically swelling and tenderness) that lasted longer then 15 days.

- There were a few occurrences of abnormal lip texture, lip firmness, lip asymmetry, lip movement, lip sensation, and mass formation. In general none of the lip assessments were remarkable or presented any safety concerns.

- The majority of *Restylane* patients experienced a palpable implant through the week 24 visit with device palpability decreasing over time (*e.g.* at week 8 the device was palpable (with an expected feel) in 92% of treated upper lips and 89% of treated lower lips. By week 24, device palpability was reported in 61% and 62% of the treated upper and lower lips, respectively). An unexpected feel was reported for 3% of the *Restylane* patients.

- The safety information on *Restylane* lip augmentation in persons of color was derived from a sample size of 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. The incidence of TEAEs reported were similar to the overall study population, with the exception of swelling which was reported more frequently in persons of color.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approvals as described above. The primary potential benefit of the device is a perceived improvement in the visual appearance of NLFs and lip fullness as assessed by GAIS and MLFS. For NLFs, improvements compared to baseline in the visual appearance as assessed using GAIS were reported by all subjects for the *Restylane-L* side of the face and 98.3% of subjects for the *Restylane* side at day 14 post-treatment. For lips, the proportion of Responders for upper and lower lips, separately and combined, for *Restylane* and No Treatment cohorts was statistically significant ($p < 0.001$) in favor of *Restylane*. For upper and lower lips combined, 92.6% (125/135) of the subjects responded to *Restylane* at week 8. In the No Treatment group,

36.4% (upper lips) and 38.5% (lower lips) of the subjects had Blinded Evaluator MLFS ratings that were at least one grade higher than baseline and 28.9% of the No Treatment subjects were Responders for both upper and lower lips combined.

Another potential benefit of adding lidocaine to *Restylane* is a reduction in pain associated with the treatment procedure. For NLFs, 71.7% of subjects had a within-subject difference in the VAS (*Restylane – Restylane-L*) pain assessment of at least 10 mm at injection. At 15 minutes post-treatment, 46.7% of subjects had a within-patient difference in VAS of at least 10 mm. At the time of treatment, the mean VAS score for *Restylane-L* was 14.7 mm compared to 44.9 mm for *Restylane*. For both treatments, all pain scores decreased over time for 60 minutes after treatment. The mean within-subject difference in VAS was statistically larger than zero at all time points ($p < 0.001$).

The willingness of a patient to accept the probable risk of a harmful event is variable and dependent on the patient's perception of benefit. The prevalence of retreatment with dermal fillers suggests that most patients are willing to take the risk of this treatment to achieve the benefit. Alternative treatments such as topical moisturizing creams, chemical or mechanical peeling procedures, and laser resurfacing are available. There were insufficient safety data to support *Restylane-L* use for lip augmentation in patients under the age of 22.

In conclusion, given the available information above, the probable benefits outweigh the probable risks for submucosal implantation for lip augmentation in patients over the age of 21.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. A perceived improvement in the visual appearance of NLFs and lip fullness was reported during the studies for more than 90% of subjects and persisted in approximately 70% of NLFs and lips at 24 weeks post-treatment. *Restylane* injection was generally well tolerated and primarily associated with mild to moderate local injection site reactions such as swelling, bruising, pain, erythema, and itching that resolved in approximately two weeks. Although rare, serious adverse events reported through postmarketing surveillance include hypersensitivity, vascular accidents, necrosis, and infection/abscess.

XIV. CDRH DECISION

CDRH issued an approval order on August 30, 2012.

The applicant's manufacturing facilities were recently inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.